## REMARKS

The issues outstanding in the Office Action mailed January 23, 2008, are the rejections under 35 U.S.C. 112, 102 and the doctrine of obviousness-type double patenting. Reconsideration of these issues, in view of the following discussion, is respectfully requested.

At the outset, it is noted that, with respect to the references crossed off on the Form-1449 accompanying Applicant's Information Disclosure, the references are those cited by the International Bureau in an international search report. As such, these references should have been furnished to the PTO. Copies of the two WO references are attached, for the PTO's convenience, inasmuch as it is assumed that these references lined off on the Form-1449 were not, in fact, transmitted by the IB. A new form 1449 listing these references is also attached. Applicants will furnish the remaining reference, as soon as it is available.

**Rejections Under 35 U.S.C. 112**

Claims 1-14 have been rejected under 35 U.S.C. 112, first paragraph. While admitting, at page 2, that the specification enables the compounds and salts thereof, it is argued that solvates and derivatives are not likewise enabled. Applicants acknowledge, as noted at page 2, that "derivatives" may include prodrugs, metabolites, etc. The apparent objection seems to be one simply of breadth and the term, rather than inability of one of ordinary skill in the art to make a specific derivative. Regardless, in order to expedite prosecution, the term "derivatives" has been removed.

With respect to the term "solvates", Applicants respectfully, albeit quite strongly, submit that the term is clearly enabled. It appears that the Office Action alleges that the formation of solvates is not enabled because, e.g., the formation of solvates is unpredictable. In support, the Office Action quotes a passage from *Vippagunta* which indicates that certain predictions about solvates or hydrates of a compound are complex and difficult.

However, the Office Action appears to ignore within the same document the passages which show the claims are enabled. For example, *Vippagunta* on page 15, top of first column, states that

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement that

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling … Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states that

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. …
> The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* throughout the reference teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof. See, e.g., pages 15-18.

While it may be true, that the prediction of what a particular solvate of a compound will actually look like, e.g., whether one, 3 ½, 6 or 12 solvent molecules are incorporated, the Office Action is incorrect with respect to the alleged lack of enablement.

Even the very paper cited in support of the rejection demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates and how such solvates would be identified or characterized, e.g., by polarized light microscopy, etc. See extensive list of techniques identified on column 2 of page 18.

Additionally, based on the above discussed statistics in this field provided by *Vippagunta*, one of ordinary skill in the art would also have a good expectation for success. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that there is no lack of enablement.

Thus, the Office Action has not carried its burden in establishing a lack of enablement

because the Office Action has not established any basis to doubt objective enablement. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971) holding that a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis added.) See also *In re Bundy*, 209 USPQ 48 (1981) holding that the "PTO must have adequate support for its challenge to the credibility of applicant's statements of utility," which statements were made in *Bundy* in the context of an enablement rejection, and which is lacking in the present case. In view of the state of the art, it is evident that there is no indication that one of ordinary skill in the art would have questioned that solvates could be formed. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005).

Nevertheless, applicants provide further information clearly demonstrating that solvate formation is a common phenomenon among pharmaceutical substances, i.e., Polymorphism: in the pharmaceutical industry (edited by *Ralf Hilfiker*; 2006 Wiley-VCH), Chapter 8, The Importance of Solvates, by *U. J. Griesser*, pp. 211-222 (hereinafter *Griesser*).

On page 220, *Griesser* teaches that

> Over almost two decades we carefully collected data on the solid-state properties of a few thousand pharmaceutically relevant organic compounds, with special focus on those drug substances listed in the Pharmacopoeia European (PhEur). The 1997 edition of PhEur contained 559 well-defined organic drug compounds. … For more than 55% of them either polymorphs or solvates are known. In a newer evaluation of a larger set of data (PhEur edition 4.02, 8008 solid organic compounds … this fraction increased only slightly to 57%. As shown in Fig. 8.4, 29% of the compounds are known to form hydrates, 10% other solvates … (Emphasis added.)

Additionally, various factors in considering whether solvates would be expected to form are identified by *Griesser* on pages 220-221, e.g., salt forms, molecular size, lipophilicity. A citation is provided for ascertaining "further trends and interrelations between molecular

properties and solvate/hydrate formation." See the middle of page 221. All this demonstrates that one of ordinary skill in the art would know or have guidance as to what factors to consider in expectation of success.

Moreover, under the section titled "Generation and Characterization of Solvates" on page 222, *Griesser* teaches that

> Since it is imperative to establish the crystal forms of an active pharmaceutical ingredient (API) to satisfy the regulatory authorities …, solvates of drug compounds are now preferentially discovered in systematic polymorph screenings. … **Automated crystallization systems and strategies** have been developed to speed up this process, **allowing thousands of crystallization experiments in a short time**. (Emphasis added.)

In view of the state of the art of solvate formation, e.g., solvate formation being a very common phenomenon associated with drug substances, the generation and examination of which is done with highly automated machines, the Office Action has not established that it would require undue experimentation by one of ordinary skill in the art to prepare and even characterize the solvates of a compound.

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take various compounds of the invention, which are explicitly admitted by the Office Action to be enabled at the top of page 3, bring them together with various solvents and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Moreover, as discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine," which it is in the present case.

Reconsideration is respectfully requested.

With respect to the preparation of stereoisomers, the comment at the bottom of page 2, paragraph 2, is not understood. One of ordinary skill in the art would clearly recognize that the claimed compounds contain chiral centers. One of ordinary skill in the art would also know, using only routine separation techniques, how to isolate givenstereo isomer. Inasmuch as such is clearly routine in the art, it is submitted that the specification clearly enables preparation of stereoisomers of the compounds of formula I. Withdrawal of this portion of the rejection is therefore also respectfully requested.

Claims 1-2 and 4-14 have also been rejected under 35 U.S.C. 112, second paragraph. Reconsideration of this rejection is respectfully requested. The issue concerning "derivatives" is moot, in view of the cancellation thereof. With respect to alcohol protecting groups, as admitted at page 3 of the Office Action, many types of protective groups for a hydroxyl group are known. It is not seen that there is any indication that Applicants do not intend to encompass all of such protecting groups. Thus, the concern expressed in the Office Action appears to be one simply of breadth, however, *In re Marzocchi* clearly states that such a concern is misplaced. Inasmuch as there are no reasons or evidence to doubt the objective enablement in the present specification, it is submitted that the recitation of "protecting groups" is clearly acceptable. Withdrawal of this rejection is also respectfully requested.

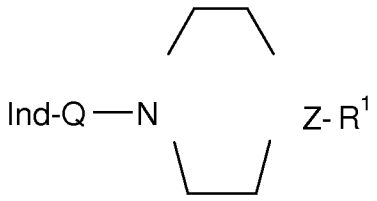
**Rejection Under 35 U.S.C. 101**

Claims 10-13 have been rejected under 35 U.S.C. 101. Reconsideration of this rejection, in view of the reformatting of the claims as method claims in consideration of U.S. practice, is respectfully requested.

**Rejections Under 35 U.S.C. 102**

Claims 1-9 and 14 have been rejected under 35 U.S.C. 102(b) over Bottcher '241. Reconsideration of this rejection is respectfully requested.

Bottcher discloses compounds of the formula




wherein "Ind" is an indol-3-yl radical which is unsubstituted or mono or polysubstitued by various moieties. It is clear from this disclosure, e.g., at column 2, defining "Ind" as an indol-3-yl radical substituted in the 5-position, and moreover by the species of the examples, which disclose 5-substituted indoles, that the patent fails to suggest indoles which are substituted on the nitrogen atom, i.e., 1-substituted. Note that the presently claimed compounds are substituted in the 1 position (on a nitrogen atom) by $R^2$, which is alkyl which may be mono or polysubstituted by halogen, or is alkaryl, alkheteroaryl, or heteroaryl. It is thus clear that the patent fails to anticipate such claims. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-3, 5-9 and 14 have been rejected under 35 U.S.C. 102(b) over Bathe (WO '794). Reconsideration of this rejection is also respectfully requested. As with Bottcher, Bathe discloses only compounds which are unsubstituted on the nitrogen atom of an indole moiety. Note that the compounds of Bathe are 5-cyano. Accordingly, the publication also fails to anticipate the present claims.

Finally, claims 1-3, 5-10 and 14 have been rejected under 35 U.S.C. 102(b) over Bartoszyk (WO '989). Reconsideration of this rejection is also respectfully requested, inasmuch as the reference also fails to disclose N-substituted indoles. Note that the '989 disclosure is directed to new indications for use of the compounds disclosed in Bottcher '241, at page 3, lines 6-10. Other compounds disclosed similarly lack the above-noted substitution. See page 2, lines 23-28, disclosing 5-cyano indols and 1H indols. Accordingly, this reference also fails to anticipate the present claims, and withdrawal of the rejection is respectfully requested.

**Double Patenting**

Claims 1 and 4-14 have been rejected under the doctrine of obviousness-type double patenting over claims 1 and 4-14 of application serial no. 10/560,734. Reconsideration of this

rejection is also respectfully requested. The compounds of the co-pending application are unsubstituted on the nitrogen atom of the fused ring. Accordingly, in the absence of any motivation for one of ordinary skill in the art to modify such compounds by providing this substitution, it is clear that the claim compounds of the application do not render the present materials obvious. Reconsideration of this rejection is thus also respectfully requested.

The claims of the application are submitted to be in condition for allowance. However, if the Examiner has any questions or comments, he or she is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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